

REMARKSRegarding the Prosecution History:

Applicants are thankful for the Examiner's diligent efforts to advance this application to allowance and are pleased to have this opportunity to address the Examiner's remaining concerns. Upon careful review of the remarks presented in this reply, the Examiner will agree that the claimed invention is patentable and that this application is in good condition for allowance.

In the final Office Action of June 22, 2007, the Examiner rejected:

- I. Claims 15 – 18 and 23 – 27 under 35 U.S.C. §103(a) over *Vallet Mas et al.* (EP 0 717 989) in view of *Redlich et al.* (US 5,225,279),
- II. Claims 19 and 20 under 35 U.S.C. §103(a) over *Vallet Mas et al.* in view of *Weitshies et al.* (US 6,068,857), and
- III. Claim 21 under 35 U.S.C. §103(a) over *Vallet Mas et al.* in view of *Liversidge et al.* (US 6,045,829).

Regarding Rejection I:

The Examiner should withdraw the rejection of claims 15 – 18 and 23 – 27 under 35 U.S.C. §103(a) over *Vallet Mas et al.* (EP 0 717 989) in view of *Redlich et al.* (US 5,225,279).

The process of claim 15, and the process by which the product of claim 26 is produced, comprise mixing an active ingredient/polymer solution or precipitate with an aqueous solution of a polymeric coating material. The specification explains that "[i]n one embodiment of the process, a molecularly disperse solution of the active ingredient in the chosen solvent is prepared together with the polymer which is to be present in the

active ingredient preparation in the core of the particles.”¹ According to independent claims 15 and 26, the active ingredient is an X-ray amorphous active ingredient, and the polymer in the active ingredient/polymer solution is one or more copolymers of acrylates, methacrylates, methacrylic acid or acrylic acid.

The combination of references, proposed by the Examiner, fails to teach or suggest the utilization of an active ingredient that is an X-ray amorphous active ingredient. The Examiner acknowledges that neither reference requires an X-ray amorphous active ingredient. Yet the Examiner takes the position that “the drug [utilized in the *Vallet Mas et al.* reference] is amorphous or at least non crystalline in nature since dissolution is not required, and the core emulsion solution is not a suspension of materials.” This argument is improper. “To establish inherency, the extrinsic evidence ‘must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.’”² A person of ordinary skill in the art would not conclude that the active ingredient utilized in the *Vallet Mas et al.* reference is necessarily an X-ray amorphous active ingredient on the basis posited by the Examiner. For this reason, the combination of references cited in this rejection fails to establish a *prima facie* case of obviousness.

The combination of references, proposed by the Examiner, also fails to teach or suggest mixing an active ingredient/polymer solution or precipitate with an aqueous solution of a polymeric coating material, wherein the polymer in the active ingredient/polymer solution is one or more copolymers of acrylates, methacrylates, methacrylic acid or acrylic acid. However, the Examiner argues that “[t]he ‘279 patent discloses core/shell particles comprising acrylate and methacrylate copolymers [and that, therefore, a] skilled artisan would be motivated to include the methacrylate polymers in order to incorporate water-insoluble active agents such as isothiazoleno.”³ The Examiner’s argument is based on an over-simplification of the cited references. When the references are considered for what they would have disclosed to a person of ordinary

¹ Page 7, lines 43 – 46, the specification.

² MPEP § 2112, citing *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

³ Page 3, lines 12 – 17 of the present Office action.

skill in the art at the time the claimed invention was made, it becomes clear that no “apparent reason to combine known elements in the fashion claimed”⁴ existed, and that the Examiner’s proposed combination would actually change the principle of operation of the inventions being modified.

The invention according to *Redlich et al.*, “provides an improved process for producing aqueous dispersions of polymeric core/shell particles prepared by sequential microsuspension polymerization having a core containing a solvent blend.”⁵ The process of *Redlich et al.* comprises:

- (a) preparing a core emulsion containing an initial monomer,
- (b) heating the core emulsion to polymerize the initial monomer, thereby forming core particles,
- (c) adding at least one base, and
- (d) optionally adding additional monomer which is polymerized on the core/shell particles.

Thus, despite the Examiner’s oversimplification of the *Redlich et al.* reference to a mere disclosure of “core/shell particles comprising acrylate and methacrylate copolymers[.]”⁶ a person of ordinary skill in the art would understand that in the *Redlich et al.* process, core/shell particles are prepared by sequential microsuspension polymerization.

On the other hand, the process disclosed in the *Vallet Mas et al.* reference involves mixing two “phases continuously while maintaining constant the relationship between the phases and the mixture volume and simultaneously spraying the resultant mixture in an evaporation system with temperature and vacuum conditions which provide for the instantaneous evaporation of the solvent from the polymer causing the deposition of the polymer around the particles or droplets.”⁷

It should be clear that the Examiner’s proposed combination involves not mere modification of, but complete abandonment of the principle of operation (sequential microsuspension polymerization) of the *Redlich et al.* process. Of course, “[i]f the proposed modification or combination of the prior art would change the principle of

⁴ *KSR Int'l v. Teleflex, Inc.*, 550 U.S. ____ (2007), Slip op. at 14, 127 S.Ct. 1727 at 1741.

⁵ Column 4, lines 44 – 48 of US 5,225,279.

⁶ Page 3, lines 12 – 13 of the present Office action.

⁷ Abstract EP 0 717 989 A1.

operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious.”⁸ For this reason, in addition to the reasons discussed above, the combination of references cited in this rejection fails to establish, a *prima facie* case of obviousness.

Indeed, a skilled artisan had no apparent reason to oversimplify the *Redlich et al.* reference to a mere disclosure of “core/shell particles comprising acrylate and methacrylate copolymers[,]”⁹ no apparent reason to abandon the principle of operation (sequential microsuspension polymerization) of the *Redlich et al.* process, and no apparent reason to make the combination/modification proposed by the Examiner. Thus, a *prima facie* case of obviousness has not been established.

Regarding Rejection II:

The Examiner should withdraw the rejection of claims 19 and 20 under under 35 U.S.C. §103(a) over *Vallet Mas et al.* in view of *Weitshies et al.* (US 6,068,857).

Claims 19 and 20 depend from claim 15. The combination of references, proposed by the Examiner, fails to teach or suggest mixing an active ingredient/polymer solution or precipitate with an aqueous solution of a polymeric coating material, wherein the polymer in the active ingredient/polymer solution is one or more copolymers of acrylates, methacrylates, methacrylic acid or acrylic acid. The Examiner has made no attempt to compensate for this shortcoming. Thus, a *prima facie* case of obviousness has not been established.

Additionally, this combination of references fails to teach or suggest the utilization of an active ingredient that is an X-ray amorphous active ingredient. As discussed regarding the previous rejection, a person of ordinary skill in the art would not conclude that the active ingredient utilized in the *Vallet Mas et al.* reference is necessarily an X-ray amorphous active ingredient on the basis posited by the Examiner. For this reason, the combination of references cited in this rejection fails to teach or suggest all of the claim limitations. Thus, a *prima facie* case of obviousness has not been established.

⁸ MPEP §2143.01, citing *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

⁹ Page 3, lines 12 – 13 of the present Office action.

Finally, in addition to being inadequate to establish a *prima facie* case of obviousness, this combination of references is insufficient to establish that which the Examiner intends. The Examiner argues that “[a] skilled artisan would be able to interchange the natural polymers of the ‘857 [*sic*] into the process of the ‘989 [*sic*] since all of the polymers are art recognized biodegradable/acceptable equivalents.”¹⁰ However, no “apparent reason to combine known elements in the fashion claimed”¹¹ existed, and the Examiner’s proposed combination would actually change the principle of operation of the inventions being modified. Indeed, the invention according to *Weitschies et al.* “relates to . . . microparticles containing active ingredients, which contain at least one gas or a gaseous phase in addition to the active ingredient(s)[,]”¹² while the process disclosed in the *Vallet Mas et al.* reference involves mixing two “phases continuously while maintaining constant the relationship between the phases and the mixture volume and simultaneously spraying the resultant mixture in an evaporation system with temperature and vacuum conditions which provide for the instantaneous evaporation of the solvent from the polymer causing the deposition of the polymer around the particles or droplets.”¹³

Regarding Rejection III:

The Examiner should withdraw the rejection of claims 21 under 35 U.S.C. §103(a) over *Vallet Mas et al.* in view of *Liversidge et al.* (US 6,045,829).

Claim 21 depends from claim 15. The combination of references, proposed by the Examiner, fails to teach or suggest mixing an active ingredient/polymer solution or precipitate with an aqueous solution of a polymeric coating material, wherein the polymer in the active ingredient/polymer solution is one or more copolymers of acrylates, methacrylates, methacrylic acid or acrylic acid. The Examiner has made no attempt to compensate for this shortcoming. Thus, a *prima facie* case of obviousness has not been established.

¹⁰ Page 5, lines 3 – 5 of the present Office action.

¹¹ *KSR Int'l v. Teleflex, Inc.*, 550 U.S. ____ (2007), Slip op. at 14, 127 S.Ct. 1727 at 1741.

¹² Abstract of US 6,068,857.

¹³ Abstract EP 0 717 989 A1.

This combination of references also fails to teach or suggest the utilization of an active ingredient that is an X-ray amorphous active ingredient. As discussed regarding the previous rejections, a person of ordinary skill in the art would not conclude that the active ingredient utilized in the *Vallet Mas et al.* reference is necessarily an X-ray amorphous active ingredient on the basis posited by the Examiner. For this reason, the combination of references cited in this rejection fails to teach or suggest all of the claim limitations. Thus, a *prima facie* case of obviousness has not been established.

Finally, in addition to being inadequate to establish a *prima facie* case of obviousness, this combination of references is insufficient to establish that which the Examiner intends. The Examiner argues that “[i]t would have been obvious to combine the stabilizers of the ‘829 patent [into] the process of the ‘989 patent in order to improve the surface stability of the nanoparticle formulation.”¹⁴ To the contrary, no “apparent reason to combine known elements in the fashion claimed”¹⁵ existed. The invention according to *Liversidge et al.* “describes formulations of nanoparticulate HIV protease inhibitors comprising a cellosic surface stabilizer.”¹⁶ According to *Liversidge et al.* particles are produced by milling the active agent in the presence of a cellosic surface stabilizer. The resulting particles contain the active ingredient in crystalline form.

Regarding the showing of unexpected results:

Since a *prima facie* case of obviousness has not been established a showing of unexpected results is in no way required, however, as expressed in the specification, “Surprisingly, the colloidal active ingredient preparations according to the invention show distinctly less growth of hydrosol particles than known active ingredient preparations which consist essentially exclusively of active ingredient mass in the core of the colloidal particles One hour after the aqueous hydrosols have been prepared in the presence of a solvent dissolving the active ingredient, the particle growth is a factor of 4 to 10 less In the case of aqueous hydrosols which contain no solvent dissolving the active

¹⁴ Page 6, lines 7 – 8 of the present Office action.

¹⁵ *KSR Int'l v. Teleflex, Inc.*, 550 U.S. ____ (2007), Slip op. at 14, 127 S.Ct. 1727 at 1741.

¹⁶ Abstract US 6,045,829.

ingredient, the particle growth is reduced by a factor of 1.5 - 5.”¹⁷

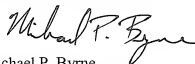
In Conclusion:

The present application is in condition for allowance. Again, applicants are thankful for the Examiner’s diligent efforts to advance this application to allowance, and request favorable action in this matter. In order to facilitate the resolution of any issues or questions presented by this paper, the Examiner is welcome to contact the undersigned by phone to further the discussion.

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¹⁷ Page 3, indicated lines 30 – 39 of the present Specification.